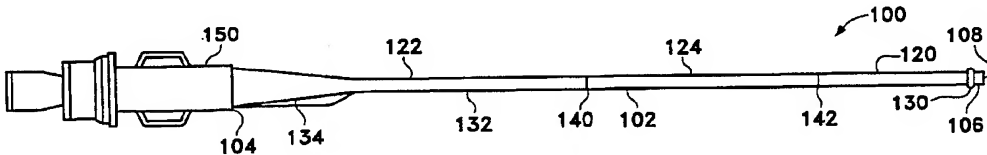


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(54) Title: METHOD FOR PRODUCING LUBRICIOUS CATHETERS			
			
(57) Abstract			
<p>This invention is in the general field of surgical instruments and, in particular, catheters. Specifically, it relates to surgical devices which have been coated on their interior with a curable lubricious polymer and to the method of making them. It relates to catheters which variously may be used in cardiovascular and endovascular procedures to deliver diagnostic, therapeutic, or vaso-occlusive agents or devices to a target site within a human or animal body and to catheters used to guide other catheters to a specific site in that body. The interior of the catheters are coated using the noted procedure in such a way that the interior is exceptionally slippery. The coating is very durable. The invention also relates to the specific methods for coating the interior of the catheters with cross-linkable polymers, preferably those which are hydrophilic or lubricious.</p>			

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5                    METHOD FOR PRODUCING LUBRICIOUS CATHETERSField of the Invention

                  This invention is in the general field of  
10    surgical instruments and, in particular, catheters.  
                  Specifically, it relates to surgical devices which  
                  have been coated on their interior with a cross-  
                  linkable lubricious polymer and to the method of  
                  making them. It relates to catheters which variously  
15    may be used in cardiovascular and endovascular  
                  procedures to deliver diagnostic, therapeutic, or  
                  vaso-occlusive agents or devices to a target site  
                  within a human or animal body and to catheters used to  
                  guide other catheters to a particular site in that  
20    body. The interior of the catheters are coated using  
                  the noted procedure in such a way that the interior is  
                  exceptionally slippery. The coating is very durable.  
                  The invention also relates to the specific methods for  
                  coating the interior of the catheters with cross-  
25    linkable polymers, preferably those which are  
                  hydrophilic or lubricious.

Background of the Invention

                  Catheters are increasingly used to deliver  
30    diagnostic or therapeutic agents and devices to  
                  internal target sites that can be accessed through the  
                  circulatory or other system. There are a number of  
                  general approaches for placing catheters within  
                  vessels in the body to reach target sites that are  
35    difficult to access. In one technique, a torqueable  
                  guidewire is introduced into the vasculature and,  
                  using radiography to monitor its advance through the  
                  body's passageways, is rotated to allow the  
                  guidewire's bent guide tip to follow a chosen route

-2-

(when a choice of pathways is found) and is advanced towards the target site. At chosen intervals during the guidewire's advancement, the catheter is slid along the guidewire until the distal end of the catheter approaches the distal end of the guidewire. This procedure is repeated until the distal end of the catheter is positioned at the target site. An example of this technique is described in U.S. Patent No. 4,884,579. This is a widely accepted and respected method for approaching target sites in complicated area of the vasculature. It, however, has the drawback of being somewhat time-consuming due to the necessity of rotating and advancing the guidewire and catheter through the vasculature.

A second technique for advancing a catheter to a target site is to use the blood flow as the motive force in placing the distal end of the catheter at the desired target site. Such methods often employ a highly flexible catheter having an inflatable, but pre-punctured balloon at its distal end. In use, the balloon is partially inflated, and carried by blood flow into the target site. During placement, the balloon is continually inflated to replenish fluid leaking from the balloon. This technique, too, has drawbacks including the fact that at least the distal portion of the catheter is so floppy that it cannot be pushed without buckling. Instead, the catheter must be advanced using injected fluid to inflate the balloon to propel the catheter to the target site. There is the additional risk of rupturing a vessel with a balloon that has been overinflated.

In order to address some of the above described problems, another approach has involved the use of flexible catheters having extremely flexible distal portions that can be directed to a target site using the blood flowing to that site as the motive force but without the use of balloons on the distal catheter tip. These flow-directed catheters have the advantage of being quite fast in that they are able to

-3-

access remote portions of the body very quickly. They carry the obvious limitation that the catheter distal tip can only go where the blood flow is the highest. Furthermore, the catheters often are limited in the size of the "load" carried to the selected site. Said another way, balloon-less flow-directed catheters may be a marginal choice if a larger embolic coil or large diameter particle is to be delivered to the select site.

10 In comparison to flow-directed catheters, over-the-wire catheters having variable stiffness (although quite strong and able to deliver embolic coils and large diameter particles through their large lumen) are comparatively quite slow in time of access. 15 Friction with the interior of the guide catheter or the vessel path considerably slows the procedure time. The time needed to push the catheter over the guidewire is often lengthy simply because of friction with the guidewire. Over-the-wire catheters have an 20 advantage in that they can be directed to portions of the vasculature inaccessible to flow-directed catheters. Lowering the resistance of the over-the-wire catheter to improve its interior or exterior lubricity and thereby, to allow improved access time 25 to remote body sites, forms a further aspect of this invention.

This invention is, generically, a catheter typically having portions of differing flexibility which is suitable for the delivery of diagnostic, 30 therapeutic, or vaso-occlusive agents or devices to potentially remote portions of the vascular system or other systems of open lumen within the body. A thin coating of a lubricious polymer is applied at least to the interior of the catheter and optionally to the 35 outside of the catheter. The preferred coating is quite slippery and is very durable.

This invention also includes a method of coating the interior of catheters using lubricious

hydrophilic polymers and a method for producing a thin layer of such polymers on polymeric substrates.

The invention also includes a method for placing the catheter at the target site and a method  
5 for delivering diagnostic, therapeutic, or vaso-occlusive agents or devices to the target site or delivering other catheters to regions near the target site.

10 Summary of the Invention

One variation of this invention is a catheter having a coated inside diameter that may be used for placement within a tortuous, small vessel pathway and a method for delivery of an agent or  
15 device to a target site. The coating is very slippery and quite durable. The catheter may be directed to the target site either by means of the blood flow to that site or by the use of a guidewire. The catheter has an elongate tubular body having proximal and  
20 distal ends and a lumen extending between the ends through which the diagnostic, therapeutic, or vaso-occlusive agent or device is delivered. Where appropriate, the lumen may be used for passage of a guidewire.

25 For this variation of the invention, the elongate tubular body may be formed of (a) a relatively stiff and, perhaps, tapered proximal segment, (b) a relatively flexible distal segment, and (c) one or more transition or intermediate sections  
30 between the proximal and distal segments that are less flexible than the distal segment but more flexible than the proximal segment. The interior of at least the distal segment and, desirably, the transition segments of the catheter are treated with a  
35 lubricious, polymeric material. The proximal section of the catheter may also be so treated. If so desired, all or part of the exterior of the catheter may be coated with the lubricious polymers.

-5-

Another variation of the invention is a flow-directed catheter. In that variation, the elongate tubular body is typically formed of a relatively stiff tapered proximal segment, a  
5 relatively flexible and strong distal segment, and a transition section between the proximal and distal segments that is less flexible than the distal segment but more flexible than the proximal segment. The distal segment often has a burst pressure of at least  
10 about 195 psi and is made of a material that will show a force of about  $1 \times 10^{-4}$  pounds of force or less when ten centimeters of the material is deflected  $10^\circ$  from horizontal.

A further variation of the invention is a  
15 guiding catheter that has been coated on its interior as described herein. These catheters are typically used in conjunction with vascular access catheters such as the guidewire-directed and flow-directed catheters and balloon catheters noted just above. The  
20 guiding catheters have inside diameters suitably sized to allow those other catheters to pass through their lumen. Such a guiding catheter may have a fairly stiff proximal section, often with a shorter straight section positioned near the distal section and often  
25 having significantly softer sections placed at the distal region and distal end. These catheters are used for quick placement, in the body, of the flow-directed or guidewire-directed catheter to a point where they are most efficient or, said another way,  
30 they act as platforms for the microcatheters or flow-directed catheters.

The interior of the catheter bodies are coated with hydrophilic polymeric materials by a method involving application of the polymer from a  
35 dilute polymer or oligomer solution desirably followed by simultaneous solvent removal and curing of the applied precursor. Curing of the catheter interior takes place by use of a quartz or glass fiber dip-leg placed within the catheter lumen. The dip-leg fiber

-6-

radiates UV radiation to the interior of the catheter and, in some instances, to the exterior of the catheter for curing the polymeric material found there. Multiple coatings of the polymeric material  
5 may be useful.

#### Brief Description of the Drawings

FIG. 1 is a diagram that shows an infusion catheter constructed according to a preferred  
10 embodiment of the present invention.

FIG. 2 is a diagram that shows the distal end on one embodiment of a flow-directed infusion catheter of the present invention in which the distal end is formed in an "S" shaped configuration.

15 FIG. 3 is a diagram showing a flow-directed infusion catheter, stylet, and guiding catheter assembly.

FIG. 4 is a side view of a typical catheter assembly according to this invention adapted for use  
20 with a guidewire.

FIG. 5A is a side view of a guiding catheter made according to this invention.

FIGS. 5B and 5C are side view, cross-sections of the tip of the guiding catheter of Fig.  
25 5A.

#### Description of the Invention

30 This invention is a catheter having an interior diameter which has been coated with a lubricious polymer and which coating has been cross-linked in situ and covalently bonded to the interior of the catheter using irradiation.

35 One variation of the inventive catheter, optionally including a guidewire, has discrete sections of varying flexibility. In one preferred variation of the invention, the catheter has a relatively stiff proximal section and a less stiff



- 7 -

mid-section. For devices intended for use as flow-directed catheters, the distal end section is quite flexible; for devices intended for use with guidewires, the distal end section need not be quite as flexible since it need only follow the path of the guidewire without substantial disturbance of that predetermined path. The various sections of the catheter may also be of variable flexibility or the entire length of the catheter may have a variable flexibility.

At least some portion of the interior portion of the catheter is coated with a polymeric material to increase its lubricity and to minimize the friction seen by the guidewire or by mechanical therapeutic or vaso-occlusive devices as they move through the catheter lumen. The mid exterior or transition section of the catheter may also be coated with the polymeric material. The proximal section exterior may also be coated although, most desirably, a small proximal end portion is left uncoated for increased control.

Another variation of the invention is a flow-directed catheter. In that variation, the elongate tubular body is typically formed of a relatively stiff tapered proximal segment, a relatively flexible and strong distal segment, and a transition section between the proximal and distal segments that is less flexible than the distal segment but more flexible than the proximal segment. The distal segment often has a burst pressure of at least about 195 psi and is made of a material that will show a force of about  $1 \times 10^{-4}$  pounds of force or less when ten centimeters of the material is deflected  $10^\circ$  from horizontal.

A further variation of the invention is a guiding catheter that has been coated on its interior as described herein. These catheters are typically used in conjunction with vascular access catheters such as the guidewire-directed and flow-directed

- 8 -

catheters noted just above. The guiding catheters have inside diameters suitably sized to allow those other catheters to pass through their lumen. Such a guiding catheter may have a fairly stiff proximal section, often with a shorter straight section positioned near the distal section and often having significantly softer sections placed at the distal region and end. These catheters are used for quick placement in the body of the flow-directed or guidewire-directed catheter to a point where they are most efficient.

#### Coatings

Particularly suitable as coatings in the catheter assembly of this invention are polymers or oligomers of monomers selected from ethylene oxide and its higher homologs including up to 6 carbon atoms; 2-vinyl pyridine; N-vinylpyrrolidone; polyethylene glycol acrylates such as mono-alkoxy polyethylene glycol mono(meth) acrylates, including mono-methoxy triethylene glycol mono (meth) acrylate, mono-methoxy tetraethylene glycol mono (meth) acrylate, polyethylene glycol mono (meth) acrylate; other hydrophilic acrylates such as 2-hydroxyethylmethacrylate, glycerylmethacrylate; acrylic acid and its salts; acrylamide and acrylonitrile; acrylamidomethylpropane sulfonic acid and its salts, cellulose, cellulose derivatives such as methyl cellulose ethyl cellulose, carboxymethyl cellulose, cyanoethyl cellulose, cellulose acetate, polysaccharides such as amylose, pectin, amylopectin, alginic acid, and cross-linked heparin; maleic anhydride; aldehydes; etc.. These monomers may be formed into homopolymers or block or random copolymers. The use of oligomers of these monomers in coating the catheter for further polymerization is also an alternative. Preferred monomers include ethylene oxide; 2-vinyl pyridine; N-vinylpyrrolidone and acrylic acid and its salts; acrylamide and

acrylonitrile each polymerized (with or without substantial crosslinking) into homopolymers, or into random or block copolymers.

Additionally, hydrophobic monomers may be included in the polymeric coating material in an amount up to about 30% by weight of the resulting copolymer so long as the hydrophilic nature of the resulting copolymer is not substantially compromised. Suitable monomers include ethylene, propylene, styrene, styrene derivatives, alkylmethacrylates, vinylchloride, vinylidenechloride, methacrylonitrile, and vinyl acetate. Preferred, because of their propensity for ease of linkage to the typical polymeric catheter substrates, are ethylene, propylene, styrene, and styrene derivatives.

Polymers or oligomers applied using the procedure described below are activated or functionalized with photoactive or radiation-active groups to permit reaction of the polymers or oligomers with the underlying polymeric surface. Suitable activation groups include benzophenone, thioxanthone, and the like; acetophenone and its derivatives specified as:



where  $\text{R}^1$  is H,  $\text{R}^2$  is OH,  $\text{R}^3$  is Ph; or  
 $\text{R}^1$  is H,  $\text{R}^2$  is an alkoxy group including -  
 $\text{OCH}_3$ ,  $-\text{OC}_2\text{H}_5$ ,  $\text{R}^3$  is Ph; or  
 $\text{R}^1 = \text{R}^2 =$  an alkoxy group,  $\text{R}^3$  is Ph; or  
 $\text{R}^1 = \text{R}^2 =$  an alkoxy group,  $\text{R}^3$  is H; or  
 $\text{R}^1 = \text{R}^2 = \text{Cl}$ ,  $\text{R}^3$  is H or Cl.

Other known activators are suitable.

The polymeric coating may then be linked with the substrate using known and appropriate techniques selected on the basis of the chosen activators preferably by ultraviolet light but also by heat or ionizing radiation. Crosslinking or curing

-10-

with the listed polymers or oligomers may be accomplished by use of peroxides or azo compounds such as acetyl peroxide, cumyl peroxide, propionyl peroxide, benzoyl peroxide, or the like. A  
5 polyfunctional monomer such as divinylbenzene, ethylene glycol dimethacrylate, trimethylolpropane, pentaerythritol di- (or tri- or tetra-) methacrylate, diethylene glycol, or polyethylene glycol dimethacrylate, and similar multifunctional monomers  
10 capable of linking the polymers and oligomers discussed above is also appropriate for this invention.

The polymeric coating may be applied to the exterior of the catheter body or other polymeric  
15 substrate by any of a variety of methods, e.g., by spraying a solution or suspension of the polymers or of oligomers of the monomers onto the catheter or by dipping the catheter into the solution or suspension (after sealing the open ends, if so desired).  
20 Initiators may be included in the solution or applied in a separate step. The catheter may be sequentially or simultaneously dried to remove solvent after application of the polymer or oligomer to the exterior of the polymeric body and crosslinked.

25

#### Procedure for Inside Diameter coating

The polymeric coating may be applied to the interior of the catheter by use of pressure forcing  
30 the precursor fluid through that interior. Because of the difficulty of achieving a reasonably smooth and even layer within that interior, it is preferred that the polymer precursor solution used for the catheter interior be cured by UV or by ionizing radiation.  
35 This is so because the polymer precursor solution should be physically stable when crosslinked. In some instances, this would mean that the solvent has been substantially removed from the layer coating the interior of the catheter. In other instances, a fluid

-11-

coating may be present on the interior, but it typically must have had the majority of the solvent removed to allow sufficient concentration of the photoactive groups to mandate the binding of the precursor to the inner catheter lumen. Thin solutions are very, very difficult to polymerize. In the latter case, if a fiber dip-leg is used to activate or cure the photoactive groups and cure the coating, the resulting coating may not be completely uniform, but nevertheless is suitable to enhance the overall slipperiness of the catheter interior. If a fluid coating is used -- one that remains liquid (albeit, a concentrated one) during the crosslinking step -- ionizing radiation may be used to polymerize the precursor solution since the radiation source does not disturb the coating.

The solution or suspension should be quite dilute since only a very thin layer of polymer is to be applied either to the interior or to the exterior of the catheter. We have found that an amount of oligomer or polymer in a solvent of between 0.25% and 5.0% (wt), preferred is 0.5 to 2.0% (wt), is excellent for thin and complete coverage of the resulting polymer. Preferred solvents for this procedure when using the preferred polymers and procedure are water, low molecular weight alcohols, especially methanol, propanol, isopropanol, ethanol, and their mixtures and ethers. Other water miscible solvents, e.g., tetrahydrofuran, methylene dichloride, methylethylketone, dimethylacetate, ethyl acetate, dimethyl acetamide, etc., are suitable for the listed polymers and must be chosen according to the characteristics of the polymer; they should be polar because of the hydrophilic nature of the polymers and oligomers but, because of the reactivity of the terminal groups of those materials, known quenching effects caused by oxygen, hydroxyl groups, and the like must be recognized by the user of this process when choosing polymers and solvent systems.

-12-

Particularly preferred as a coatings for the catheter bodies discussed below are physical mixtures of homo-oligomers of at least one of polyethylene oxide; poly 2-vinyl pyridine; polyvinylpyrrolidone, 5 polyacrylic acid, polyacrylamide, and polyacrylonitrile.

#### Exterior Coating

When applying a polymeric coating to the 10 exterior of the catheter, the catheter bodies or substrates are preferably sprayed or dipped, dried, and irradiated to produce a polymerized and cured and bonded polymeric skin of the noted monomers or oligomers. The exterior lubricious hydrophilic 15 coating is preferably produced using generally sequential solvent removal and crosslinking operations. The coating is applied at a rate allowing "sheeting" of the solution, e.g., formation of a visibly smooth layer without "runs". In a dipping 20 operation for most polymeric substrates noted below, the optimum coating rates are found at a linear removal rate between 0.25 and 2.0 inches/sec, preferably 0.5 and 1.0 inches/sec.

The solvent evaporation operations may be 25 conducted using a heating chamber suitable for maintaining the surface at a temperature between 25°C and the glass transition temperature ( $T_g$ ) of the underlying substrate. Preferred temperatures are 50°C to 125°C. Most preferred for the noted and preferred 30 solvent systems is the range of 75° to 110°C.

Ultraviolet light sources may be used to crosslink the polymer precursors onto the substrate polymeric device. Movement through an irradiation chamber having an ultraviolet light source at 90-375nm 35 (preferably 300-350nm) having an irradiation density of 50-1200 mW/cm<sup>2</sup>, preferably 50-300 mW/cm<sup>2</sup>, most preferably 150-250 mW/cm<sup>2</sup> for a period of three to seven seconds is desired. Passage of a catheter through the chamber at a rate of 0.25 to 2.0

-13-

inches/second (0.5 to 1.0 inches/second) in a chamber having three to nine inches length is suitable. When using ionizing radiation, a radiation density of 1 to 100 kRads/cm<sup>2</sup> (preferably 20 to 50 kRads/cm<sup>2</sup>) may be applied to the solution or suspension on the polymeric substrate.

In sum, the process preferably involves the substantive steps of creating a coating of substantial uniformity, drying, and then curing the coating using ultraviolet radiation to produce a coating which is covalently bonded to the substrate.

Exceptional durability of the resulting coating is produced by repetition of the dipping/solvent removal/irradiation steps up to five times. Preferred are two to four repetitions.

#### Interior Coating

As was the case with applying the polymer precursor to the exterior of the catheter, the solution or suspension of the polymer precursor should be quite dilute. The amount of oligomer or polymer in a solvent may desirably be between 0.10% and 5.0% (wt), preferred is 0.10% to 2.5% (wt) to assure coverage of the interior surface of the catheter. A small amount of a flow additive is also desirable. It must be remembered that the interior diameter of many catheters is perhaps as small as 0.008 inches.

Solvents suitable for this operation are the same as those listed for exterior coating although there is a preference for low molecular weight solvents to lower the overall viscosity of the precursor solution.

Similarly, the polymer precursors listed for use as exterior catheters are also suitable for interior coating.

As was noted above, the coating is preferably applied using a pressurized source to pass the precursor solution through the catheter. Once the

-14-

catheter is filled. The solution is then expressed to allow the solution to coat the interior but not to form plugs or the like.

Heated air (e.g., at 250°-350° F) may be introduced into the region of the catheter perhaps with added direct heat, to remove the solvent, and leave a thin coat behind. If a uniform coating is necessary, this step must be carried out at a proper rate to form that uniform coating prior to the irradiation step.

A fused silica (glass or quartz) fiber dip-leg coupled to a UV source is then passed through the catheter lumen at a rate appropriate for crosslinking the polymer. The dip-leg fiber may be coupled to a UV source such as a short-arc mercury lamp or laser. The dip-leg is configured so that the major portion of the UV passes through the tip onto the interior of the catheter lumen. Reflective fibers are excellent for this service.

The dip-leg fiber is moved at a rate proportional to the cross-sectional ID area. For instance, for a catheter having a 0.047" ID, a 1000 watt short arc mercury lamp joined to a fused quartz fiber, the rate would be about 17"/minute.

The steps of coating, dying, and cross-linking may be repeated for two or more iterations.

#### Variations of the Inventive Catheter

FIG. 1 shows an infusion catheter (100) constructed according to one embodiment of the invention. The catheter (100) has an elongate tubular body (102) with proximal (104) and distal (106) ends and an open inner lumen (108) extending between the ends. The elongate tubular body (102) has three segments; a relatively flexible and strong distal segment (120), a relatively stiff tapered proximal segment (122) and a transition section or segment (124) between the proximal and distal segments that is



-15-

less flexible than the distal segment (120) but more flexible than the proximal segment (122).

The elongate tubular body (102) has a strong distal segment (120) which is desirably "relatively flexible" such that the catheter can easily navigate a tortuous vessel pathway. By "relatively flexible" is meant that, at 10 cm., a force of about  $1 \times 10^{-4}$  pounds corresponds to a deflection of the material that is  $10^\circ$  from horizontal, or only about  $5 \times 10^{-4}$  pounds of force to deflect the material about  $80^\circ$  from horizontal. By "relatively strong" is meant that the material has a burst pressure of greater than 195 psi, more preferably, the burst pressure is between about 195 and 220 psi.

The flexible distal segment (120) has an open end which allows for the infusion of diagnostic, therapeutic, or vaso-occlusive agents into the target site. When the catheter is a flow-directed infusion catheter, the flexible distal segment (120) preferably is made of a polymer that is springy and biologically compatible such as low density polyethylene, polyurethane, a block copolymer of polyamide, polyvinyl chloride, or silicone, or blends of the above.

The flexible distal segment (120) may carry one or more radiopaque bands (130) or may be doped with a radiopaque material such as barium sulfate, bismuth trioxide, bismuth carbonate, tungsten, tantalum or the like so that the location of the distal region of the catheter within the vessel may be visualized radiographically. The distal segment (120) typically makes up between about 5 and 25% of the total length of the tubular member and is between about 5 and 40 cm long, preferably between about 10 and 20 cm long. The inner diameter of the distal segment (120) may be between about 0.25 and 0.50 mm, more preferably between about 0.25 and 0.35 mm. The outer diameter of the distal segment may be between about 0.50 and 0.80 mm, more preferably between about

-16-

0.60 and 0.70 mm. The wall thickness of the distal segment 120 is between about 0.1 and 0.3 mm.

The proximal segment (122) of the elongate tubular body (102), when used as a flow-directed  
5 infusion catheter, is relatively stiff so that it can be easily pushed and thus eliminate need for guidewire support. The proximal segment (122) may be made of a polymeric or metallic material that is relatively stiff and biologically compatible, e.g., high density  
10 polyethylene, polypropylene, polyamides such as Nylons, polyurethane, polyimides, polyvinyl chloride, polysulfones, polyfluorocarbons, polyethylene terephthalate, their mixtures, copolymers; or polyester elastomers or a braided shaft (a polymer  
15 outer core with a metallic mesh inner core). The proximal segment (122) may comprise a tapered proximal section (134) for attachment to the proximal end fitting (150) and a distal section (132). The proximal section (134) of proximal segment (122) may  
20 make up between about 60% and 80% of the total length of the tubular member (102) and typically is between about 90 and 130 cm long, preferably between about 100 and 120 cm long. The largest inner diameter of the proximal section (134), measured at the proximal end  
25 (104) of the tubular member (102), is often between about 0.40 and 0.60 mm, more preferably between about 0.45 and 0.55 mm. The outer diameter of the proximal section (134) at the proximal end (104) of the tubular member (102) is between about 0.8 and 1.2 mm. The  
30 wall thickness of the proximal section (134) of proximal segment (122) is between about 0.1 and 0.4 mm, more preferably between about 0.2 and 0.3 mm.

The distal section (132) of proximal segment (122) makes up between 10 and 20% of the total length  
35 of the tubular body (102) and is between about 20 and 40 cm long, preferably between about 20 and 30 cm long. The inner diameter of the distal section (132) of proximal segment (122) may be between about 0.20 and 0.50 mm, more preferably between about 0.25 and

-17-

0.35 mm. The outer diameter of the distal section (132) of proximal segment (122) is between about 0.60 and 0.90 mm, more preferably between about 0.60 and 0.70 mm. The wall thickness of the distal section (134) of proximal segment (122) is typically between about 0.1 and 0.3 mm.

The transition section (124) of the elongate tubular body (102) is less stiff than the proximal segment (122) but more stiff than the distal segment (120). A suitable material that is biologically compatible is a polymer such as polyurethane, a block copolymer of polyamide, polyvinyl chloride or silicone with greater durometer reading (i.e. that is stiffer) than the flexible distal segment (120). The transition section (124) may be radiopaque and thus observable in the event that the catheter becomes lodged in a particular portion of the vasculature or buckles. The polymeric material may be doped with a radiopaque material such as barium sulfate, bismuth carbonate, bismuth trioxide, tungsten, tantalum or the like. Bismuth trioxide is not always color-stable when exposed to ultraviolet light and may not be a wise choice if color-fastness is a desirable choice. The transition section (124) may make up between about 10 and 20% of the total length of the tubular member (102) and is between about 20 and 40 cm long, preferably between about 25 and 35 cm long. The transition section (124) may be of constant diameter or may be tapered. The inner diameter of the transition section (124) may be between about 0.20 and 0.50 mm, more preferably between about 0.20 and 0.35 mm. The outer diameter of the transition section (124) may be between about 0.50 and 0.90 mm, more preferably between about 0.60 and 0.70 mm. The wall thickness of the transition section (124) may be between about 0.1 and 0.3 mm.

The proximal segment (122), transition section (124), and distal segment (120) are joined at junctions (140) and (142), respectively. The

-18-

junctions may be formed by flaring, overlapping, and heat fusing the materials of the proximal segment (122) and transition section (124) and the transition section (124) and distal segment (120). Other methods  
5 for forming the junction, e.g., heat welding, solvent welding, etc. are also suitable. The distal segment (120), transition section (124) and distal section (132) of proximal segment (122) may all have approximately the same outside diameter or the  
10 transition section (124) and the distal section (132) of the proximal segment (122) may be tapered.

A standard proximal end fitting (150) may be attached to the proximal end (134) of the proximal segment (122) often by gluing or by heat fusion with  
15 reinforcing tubing.

The lumen of these catheter embodiments extends from the distal end (108), through distal section (120) through midsection (124) and through proximal section (122). It is this lumen which is to  
20 be coated with the polymeric material discussed herein to improve its lubricity.

FIG. 2 shows an embodiment of the distal segment (120) of the catheter where the tip (160) of the catheter is pre-shaped by heating with steam so  
25 that the distal end (106) points towards the wall of the vessel rather than in the direction of blood flow to increase the ease of manipulation through the tortuous vessel pathway. The particular embodiment shown is an "S" shape, but the tip may be any shape  
30 that allows for access to the particular vasculature being treated. One additional shape is that of a hockey stick. In this way, if the catheter becomes lodged against the vessel wall, the infusion of liquid through the catheter propels the distal end (106) of  
35 the catheter away from the vessel wall. Since the stiff proximal segment (122) is pushed, the distal segment (120) will be carried by the blood flood to the target site.

-19-

The catheter described above is useful in delivering diagnostic, therapeutic, or vaso-occlusive agents and devices to deep tissue, usually without need for a guidewire.

5           FIG. 3 shows a catheter assembly (200) for placing the infusion catheter (100) at the target site. An appropriate guiding catheter (202) is inserted into the vasculature using standard placement techniques. A rotating hemostatic valve (204) may be  
10 utilized by connection to the guiding catheter luer adapter (206). The guiding catheter (202) is continuously flushed with saline. The thumb-screw of the valve (204) is opened and the infusion catheter (100) is inserted through the rotating hemostatic  
15 valve (204). Optionally, as shown in FIG. 3, a Teflon-coated stainless steel stylet (208) is first inserted into the flow-directed infusion catheter (100) in order to prevent kinking of the infusion catheter (100) within the valve (204). The distal end  
20 (106) of the infusion catheter (100) is advanced proximal to the tip of the guiding catheter (202). The stylet (208) is then removed from the infusion catheter (100). Once the stylet (208) is removed, the infusion catheter (100) is pushed out of the guiding  
25 catheter (202). The flow-directed infusion catheter (100) is gently guided by the flow of blood in the vasculature to the target site. Optionally, gentle pushing and pulling and injection of saline or contrast medium through the catheter lumen (108) may  
30 aid in the placement of the catheter at the target site.

Once at the target site, the desired agent is injected. Such agents may include radiopaque agents for viewing blood vessel anatomy and blood flow  
35 characteristics in the target region, vaso-occlusive agents which can be used to produce small-artery vaso-occlusion in the tissue region supplied by the target vessel, and pharmacological agents, such as anti-tumor drugs or sclerosing agents such as alcohols, which are

-20-

effective against identified disease states at the target site. Vaso-occlusive agents useful in the treatment of arteriovenous malformations include polymers that are activated in the presence of polar solvents such as water and include materials such as n-butylcyanoacrylate. Other types of vaso-occlusive agents useful in the treatment of arteriovenous malformations include polymer solutions that coagulate by diffusion of the solvent when in contact with blood. Polyvinyl acetate dissolved in dimethylsulfoxide is one such agent. Alternatively, vaso-occlusive coils may be injected into the infusion catheter and delivered to a target site to occlude the blood flow at that site.

Figure 4 shows a variation of the invention in which the catheter is guided to its intended site by the use of a guidewire rather than through the use of blood flow. As with the device described above, the catheter assembly (400) includes an elongate member (402) having a proximal end (404) and a distal end (406) and an inner lumen which extends between those two ends. It is this lumen which is to be coated with the polymeric material discussed herein to improve its lubricity. The elongate tubular body (402) has three segments; a relatively flexible distal segment (408), a relatively stiff proximal segment (410) and a transition section or middle segment (412) (separated at junction (414) from the proximal segment) between the proximal and distal segments that is less flexible than the distal segment (408) but more flexible than the proximal segment (410). Found within the lumen of the catheter assembly is guidewire (414) often having a bent tip (416) to allow ease of passage through the vasculature. The guidewire itself may also be treated with the materials discussed herein to improve its lubricity. Typically, such a catheter will have a small radiopaque band (418) of gold, platinum, palladium, or the like to permit monitoring of the catheter tip's position in relation

-21-

to the tip of the guidewire or, when the guidewire is not in the catheter, to the vasculature itself. A standard proximal end fitting (420) may be attached to the proximal end (404) of the proximal segment (410) often by heat fusion with reinforcing tubing. As is described in U.S. Pat. No. 4,739,768, to Engelson, the variation of flexibility may be introduced into the catheter assembly by use of sections of discrete coaxial tubing, e.g., by use of an inner stiff tube of polypropylene or high density polyethylene covered by a flexible tube of low density polyethylene or silicone in the proximal section (410) with the inner tubing junction found at (410). A thinner wall inner tubing of the same polymer as found in the proximal section (410) may be used as the inner tubing in middle section (412) to provide decreased stiffness in the middle section (412). In such an instance, the outer coaxial layer could be of the same composition and dimensions from proximal end (404) to distal end (406). Other methods of varying the stiffness to provide for strength at the proximal end, extreme flexibility at the distal end to allow conformance to the contortions of the guidewire through multiple flexions, and a middle section of strength sufficient to transmit pressure and torque from proximal end to distal end without buckling or compression. The various sections (particularly the inner section) may be tapered to provide variable stiffness through at the section or throughout the catheter.

Figure 5A shows still another variation of the inventive catheter. In this instance, the device is a guiding catheter (500). As was discussed above, a guiding catheter is an intravascular catheter used as the conduit for other catheters to traverse the distance between the entrance site (usually with the assistance of an introducer) at the exterior of the body to near the site where the micro-catheter is to be used. Consequently, the interior diameter of the guiding catheter is larger than the exterior diameters

-22-

of the catheters discussed above. These catheters, as a group, are well known. However we have invented a guiding catheter with special properties, such properties including interior lubricious coatings as  
5 have been discussed above.

Specifically, the guiding catheter (500) of this invention has a tubular body having a lumen extending from its distal end to its proximal end. Through this lumen, the interior catheter extends.  
10 The catheter is formed of four generally distinct sections: the distal section (502), the intermediate section (504), the narrow proximal section (504), and the wide proximal section (508). In total, the length of the catheter is typically between 70 and 120 cm.

15 The distal section (502) must be reasonably stiff but of a soft material to prevent damage to the interior of the blood vessels after it is inserted and is being forwarded to its selected point. The distal section (502) is preferably of a material having a  
20 Durometer reading of 80 to 100 on the Shore "A" scale, a flexural modulus (ASTM D790) of 3000 psi to 10000 psi, and an ultimate tensile strength (ASTM D412) of at least 7000 psi. Our preferred material for this portion of the device is a polyurethane such as  
25 Thermedics Tecothane 1095A. It is preferred that the polymer making up this portion of the device filled with an x-ray opaque filler such as bismuth trioxide, barium sulfate, tantalum powder, tungsten powder, or other known opacifiers. For our catheter, we prefer  
30 tungsten powder.

The catheter midsection (504) preferably is of a material which forms a transition between the stiffer proximal sections (506, 508) and the softer distal section (502) both in stiffness and in size.  
35 It is chosen of a material which is miscible or bondable with the materials in the neighboring sections. We prefer a material having a Durometer reading of 45 to 60 on the Shore "D" scale, a flexural modulus (ASTM D790) of 10,000 psi to 35,000 psi, and



-23-

an ultimate tensile strength (ASTM D412) of at least 7000 psi. Our preferred materials for this portion of the device are selected from a polyurethanes such as Thermedics Tecothane 1055D and polyether block amides (PEBA) such as ATOCHEM PEBAX 5533. The latter is preferred. It again preferred that the polymer making up this portion of the device be filled with an x-ray opaque filler such as bismuth trioxide, barium sulfate, tantalum powder, tungsten powder, or other known opacifiers. For this section, we prefer barium sulfate to differentiate it from the section more distal. The inside diameter of the midsection (504) is, like the distal section (502), about 40 to 50 mils. The outside diameter of the midsection (504) is, like the distal section (502), about 65 to 80 mils. The total length of the midsection (504) and the distal section (502) is usually no more than about 2-12 cm.

As an aside, the polyurethanes noted herein have been considered to be comparatively sticky and consequently a questionable choice for devices which must undertake sliding as a part of the device's function. The addition of the coating specified herein permits the polymer to be used in such service.

The narrow proximal section (506) is of the same general inside and outside diameter as are the midsection (504) and the distal section (502). For this and the wide proximal section, we prefer a material having a flexural modulus (ASTM D790) in excess of 90,000 psi and an ultimate tensile strength (ASTM D412) of at least 8500 psi. Our preferred materials for this portion of the device are selected from a Nylon 12 such as those sold by ATOCHEM in the Rilsan line and polyether block amides (PEBA) such as PEBAX 1147. The latter is preferred. For these sections, we prefer barium sulfate as the opacifier.

Finally, the wide proximal section (508) is made up of the same materials as is the narrow proximal section. It differs from the narrow proximal

-24-

section in that it has an outside diameter of at least about 80 mils.

Another alternative of the guiding catheter involves a proximal section which is not of the two diameter version discussed above. For instance, the proximal section may be of constant diameter and produced from the polymers discussed above. The proximal section may be of a multilayer construction such as that discussed above with respect to the guidewire-guided catheter. The proximal section may be braided and formed of a coated fibrous braid, all of the cited stiffness. The braid may be placed between two coaxial layers of tubing.

Figure 5B shows a close-up cross section of a distal tip (510) in which the tip is chamfered to prevent trauma as the catheter is advanced through the vasculature. The taper of the angle on that tip (510) is generally from 12 to 25°, with 15±1° preferred.

Figure 5C shows a close-up cross section of a distal tip (512) in which the tip is radiused to prevent trauma as the catheter is advanced through the vasculature.

The interior of the catheter is coated with the same materials and in the same way as are the other catheters discussed above.

Although preferred embodiments of the invention have been described herein, it will be recognized that a variety of changes and modifications can be made without departing from spirit of the invention as found in the claims which follow.

-25-

We Claim As Our Invention:

1. A catheter comprising an elongate tubular member having proximal and distal ends, an inner lumen extending between these ends, and a  
5 polymeric, lubricious coating on at least a portion of the inner lumen, which coating has been covalently bonded to the inner lumen in-situ with irradiation.
2. The catheter of claim 1 wherein the  
10 whole of the inner lumen is coated with a polymeric, lubricious coating.
3. The catheter of claim 1 wherein the catheter has an exterior surface and that exterior is  
15 at least partially coated with a polymeric, lubricious coating.
4. A catheter assembly, said catheter comprising an elongate tubular member having proximal  
20 and distal ends, an inner lumen and an exterior surface extending between these ends, said member comprising:
  - (a) a relatively stiff proximal segment;
  - (b) a relatively flexible distal segment;
  - 25 and
  - (c) a transition section between said proximal and said distal segments that is less flexible than the distal segment but more flexible than the proximal segment, and
  - 30 (d) a polymeric, lubricious coating on at least a portion of the inner lumen, which coating has been covalently bonded to the inner lumen in-situ.
5. The catheter of claim 4 where the whole  
35 of the inner lumen is coated with a polymeric, lubricious coating.

-26-

6. The catheter of claim 4 where the catheter exterior surface is at least partially coated with a polymeric, lubricious coating.

5           7. The catheter of claim 6 where at least a portion of the exterior surface of the distal segment is coated with a polymeric, lubricious coating.

10           8. The catheter of claim 6 where the exterior surface of the distal segment and the transition segment is coated with a polymeric, lubricious coating.

15           9. The catheter of claim 6 where at least a portion of the exterior surface of the proximal segment is coated with a polymeric, lubricious coating.

20           10. The catheter of claim 4 in which the coating is a polymer or oligomer comprising monomers selected from at least one of ethylene oxide; 2-vinyl pyridine; N-vinylpyrrolidone; polyethylene glycol acrylates, 2-hydroxyethylmethacrylate,  
25   glycerylmethacrylate; acrylic acid and its salts, acrylamide and acrylonitrile; acrylamidomethylpropane sulfonic acid and its salts; cellulose, cellulose derivatives such as methyl cellulose ethyl cellulose, carboxymethyl cellulose, cyanoethyl cellulose,  
30   cellulose acetate, polysaccharides including amylose, pectin, amylopectin, alginic acid, and cross-linked heparin.

35           11. The catheter of claim 4 in which the coating is a polymer or oligomer comprising monomers selected from mono-alkoxy polyethylene glycol mono(meth) acrylates, including mono-methoxy triethylene glycol mono (meth) acrylate, mono-methoxy

-27-

tetraethylene glycol mono (meth) acrylate,  
polyethylene glycol mono (meth) acrylate.

12. The catheter of claim 4 wherein the  
5 distal segment has a burst pressure of at least about  
195 psi and is made of a material which will show a  
force of about  $10^{-4}$  pounds or less when ten centimeters  
of the material is deflected  $10^\circ$  from horizontal.

10 13. The catheter of claim 12 wherein the  
burst pressure of the distal segment is between about  
195 and 220 psi.

14. The catheter of claim 13 wherein the  
15 distal section is made of a material that further will  
show an additional force of about  $10^{-5}$  pounds or less  
for each  $1^\circ$  of deflection of the material from  
horizontal.

20 15. The catheter of claim 4 wherein the  
proximal segment is made of a polymeric material  
selected from the group consisting of polyethylene,  
polypropylene, nylon, polyvinyl chloride, polyethylene  
terephthalate or other polyester elastomer or of a  
25 polymer outer core with a metallic mesh inner core and  
laminates thereof.

16. The catheter of claim 4 wherein the  
distal segment is made of a polymeric material  
30 selected from the group consisting of polyethylene,  
polypropylene, polyurethane, a block copolymer of  
polyamide, polyvinyl chloride, silicone and blends  
thereof.

35 17. The catheter of claim 4 wherein the  
polymeric material of the distal segment is mixed with  
a radio opaque material selected from the group  
consisting of barium sulfate, bismuth trioxide,  
bismuth carbonate, tungsten, and tantalum.

-28-

18. The catheter of claim 4 wherein the transition section is made of a polymeric material selected from the group consisting of polyethylene, polypropylene, polyurethane, a block copolymer of  
5 polyamide, polyvinyl chloride, and silicone, and laminates thereof.

19. The catheter of claim 4 wherein the polymeric material of the transition section is mixed  
10 with a radio opaque material selected from the group consisting of barium sulfate, bismuth trioxide, bismuth carbonate, tungsten, and tantalum.

20. The catheter of claim 4 wherein the  
15 distal segment is in an S-shaped or hockey stick shaped configuration.

21. A guiding catheter comprising an elongate tubular member having proximal and distal  
20 ends, an inner lumen and an exterior surface extending between these ends, said member comprising:

- (a) a relatively stiff proximal segment;
- (b) a relatively flexible distal segment;

and

25 (c) a transition segment between said proximal and said distal segments that is less flexible than the distal segment but more flexible than the proximal segment, and

(d) a polymeric, lubricious coating on at  
30 least a portion of the inner lumen, which coating has been covalently bonded to the inner lumen in-situ using UV radiation.

22. The guiding catheter of claim 21 where  
35 the whole of the inner lumen is coated with a polymeric, lubricious coating.

-29-

23. The guiding catheter of claim 21 where the catheter exterior surface is at least partially coated with a polymeric, lubricious coating.

5           24. The guiding catheter of claim 21 where the distal section is a polyurethane having a Durometer reading of 80 to 100 on the Shore "A" scale, a flexural modulus (ASTM D790) of 3000 psi to 10000 psi, and an ultimate tensile strength (D412) of at  
10       least 7000 psi.

          25. The guiding catheter of claim 21 where the transition section is a polyurethane or polyether block amides (PEBA) having a Durometer reading of 45  
15       to 60 on the Shore "D" scale, a flexural modulus (ASTM D790) of 10,000 psi to 35,000 psi, and an ultimate tensile strength (ASTM D412) of at least 7000 psi.

          26. The guiding catheter of claim 21 where  
20       the proximal segment is a Nylon 12 or polyether block amide (PEBA) having a flexural modulus (ASTM D790) in excess of 90,000 psi and an ultimate tensile strength (ASTM D412) of at least 8500 psi.

25           27. The guiding catheter of claim 21 in which the coating is a polymer or oligomer comprising monomers selected from at least one of ethylene oxide; 2-vinyl pyridine; N-vinylpyrrolidone; polyethylene glycol acrylates, 2-hydroxyethylmethacrylate,  
30       glycerylmethacrylate; acrylic acid and its salts, acrylamide and acrylonitrile; acrylamidomethylpropane sulfonic acid and its salts; cellulose, cellulose derivatives such as methyl cellulose ethyl cellulose, carboxymethyl cellulose, cyanoethyl cellulose,  
35       cellulose acetate, polysaccharides including amylose, pectin, amylopectin, alginic acid, and cross-linked heparin.

-30-

28. The guiding catheter of claim 21 in which the coating is a polymer or oligomer comprising monomers selected from mono-alkoxy polyethylene glycol mono(meth) acrylates, including mono-methoxy  
5 triethylene glycol mono (meth) acrylate, mono-methoxy tetraethylene glycol mono (meth) acrylate, polyethylene glycol mono (meth) acrylate.

29. The guiding catheter of claim 21  
10 wherein the polymeric materials comprising the proximal segment; the distal segment; and transition segment between said proximal and said distal segments are mixed with a radio opaque material selected from the group consisting of barium sulfate, bismuth  
15 trioxide, bismuth carbonate, tungsten, and tantalum.

30. A method for producing a thin coating of a covalently bonded polymer coating on a polymeric substrate which is the interior of an elongated  
20 tubular member, which process comprises the steps of:

- a.) applying a dilute solution or suspension of a solvent and a polymer or oligomer to a selected polymeric substrate to form a  
25 sheet comprising said solvent and polymer or oligomer,
- b.) removing at least a substantial portion of the solvent from the sheet, and
- 30 c.) introducing a fiber optic dip-leg into the interior of the tubular member and curing said polymer or oligomer by ultraviolet radiation emanating from said dip-leg so to  
35 covalently bond said polymer to the interior of the tubular member.



-31-

31. The method of claim 30 additionally comprising the steps of sequentially repeating steps a.) and b.) up to four times prior to step c.).

5                   32. The method of claim 30 where the polar solution comprises a solvent selected from ethers, alcohols, water, and mixtures.

10                   33. The method of claim 32 where the polar solution comprises a solvent selected from methanol, ethanol, isopropanol, water, and mixtures.

15                   34. The method of claim 32 where the polar solution contains 0.25% to 5.0% (wt) of polymer precursor.

20                   35. The method of claim 34 where the polar solution contains 0.25% to 2.5% (wt) of polymer precursor.

25                   36. The method of claim 30 where the polymer precursor solution contains polymers or oligomers of monomers selected from ethylene oxide; 2-vinyl pyridine; N-vinyl pyrrolidone; polyethylene glycol acrylates including  
monoalkoxypolyethyleneglycolmono(meth) acrylate,  
monomethoxytriethyleneglycolmono(meth) acrylate,  
monomethoxytetraethyleneglycolmono(meth) acrylate,  
polyethyleneglycolmono(meth) acrylate; hydrophilic  
30 acrylates such as 2-hydroxyethylmethacrylate, glycerylmethylacrylate, acrylic acid and its salts; acrylamide and acrylonitrile; acrylamidomethylpropane sulfonic acid and its salts; cellulose, cellulose derivatives, methyl cellulose, ethyl cellulose,  
35 carboxymethyl cellulose, cyanoethyl cellulose, cellulose acetate, polysaccharides such as amylose, pectin, amylopectin, alginic acid, and cross-linked heparin.

-32-

37. The method of claim 30 where the temperature of the solvent removal step is between 25° C and the glass transition temperature of the polymeric substrate.

5

38. The method of claim 37 where the temperature of the solvent removal step is between 50° C and 125° C.

10

39. The method of claim 30 where the curing step comprises the application of ultraviolet light at a radiation density of 100 to 1200 mW/cm<sup>2</sup> to the polymeric substrate.

15

40. The method of claim 39 where the curing step comprises the application of ultraviolet light at a radiation density of 150 to 250 mW/cm<sup>2</sup> to the polymeric substrate.

20

25

30

35

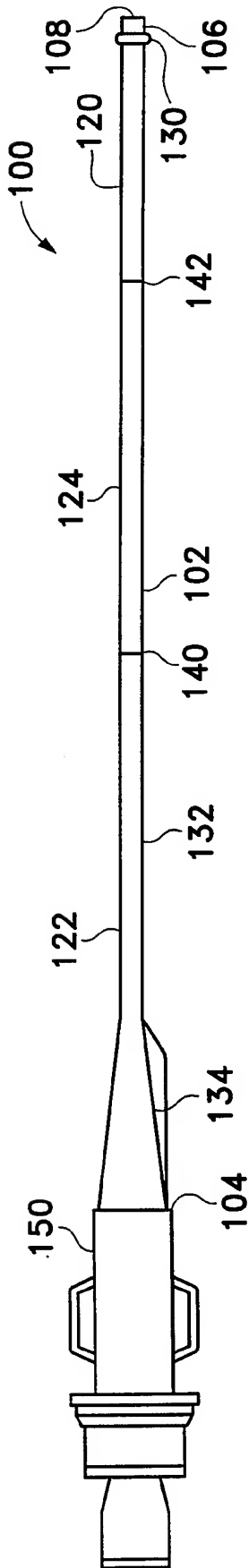


FIG. 1

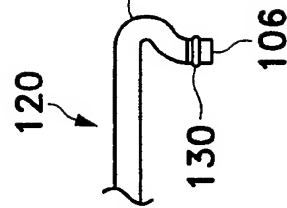


FIG. 2

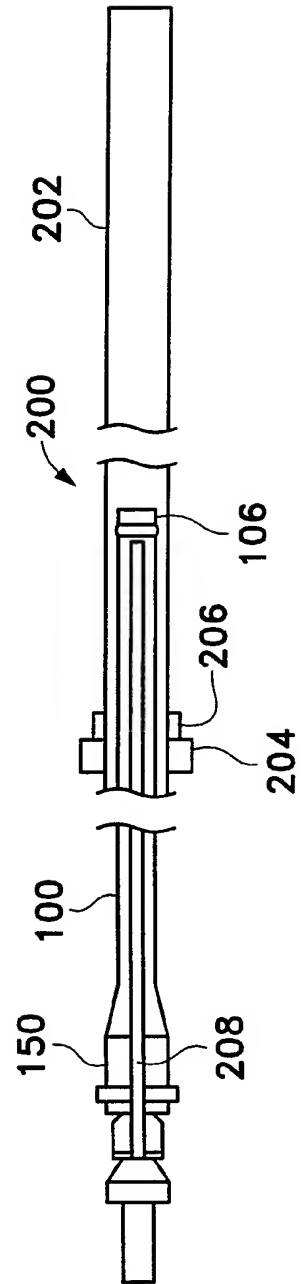


FIG. 3

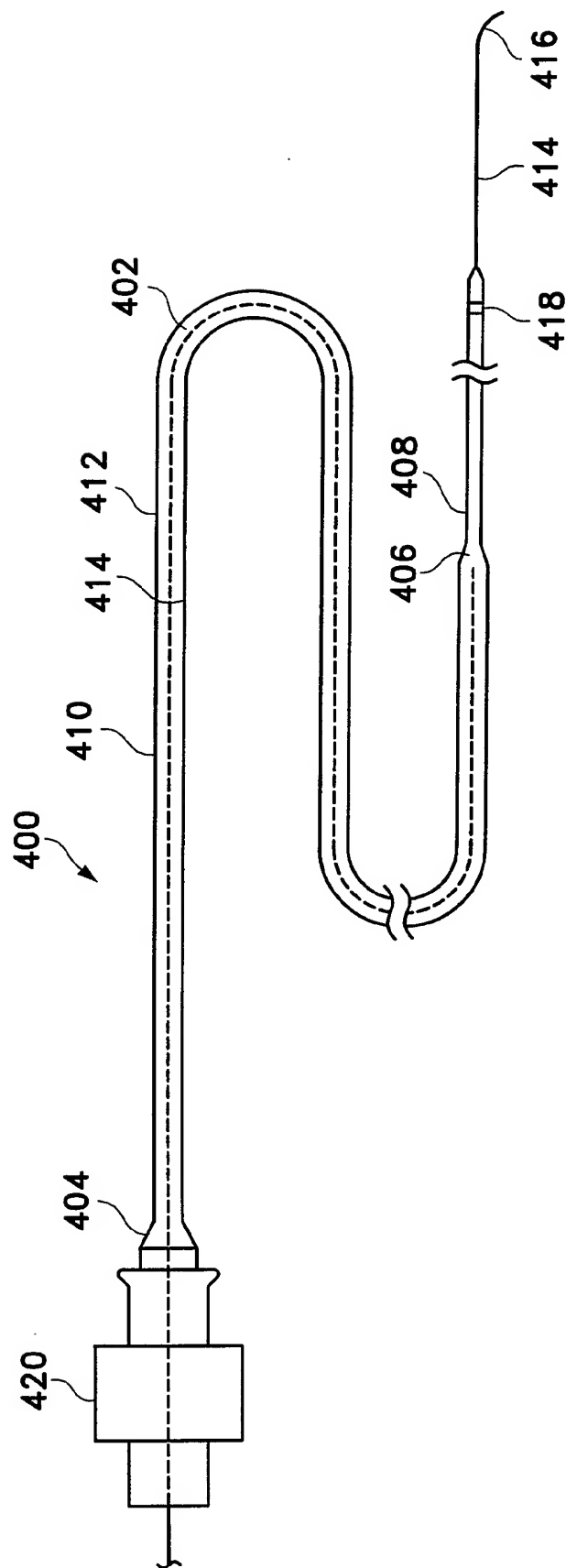


FIG. 4

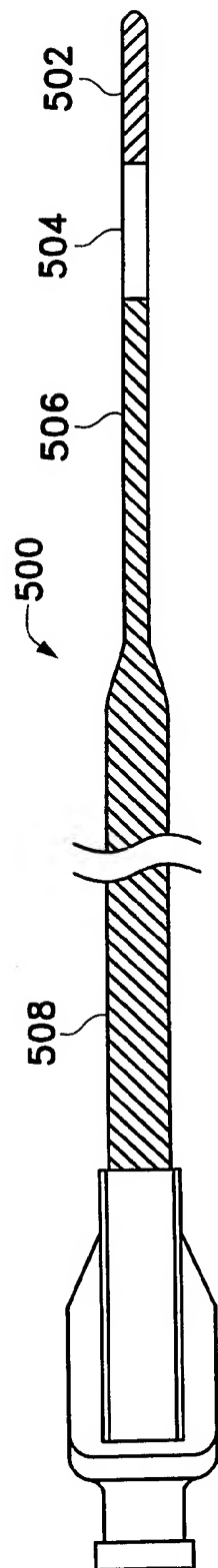


FIG. 5A

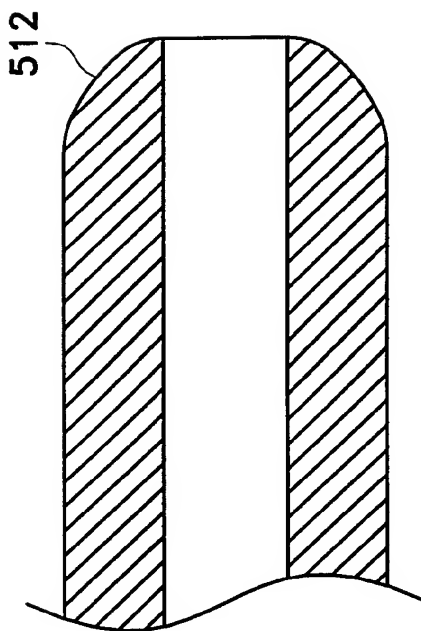


FIG. 5C

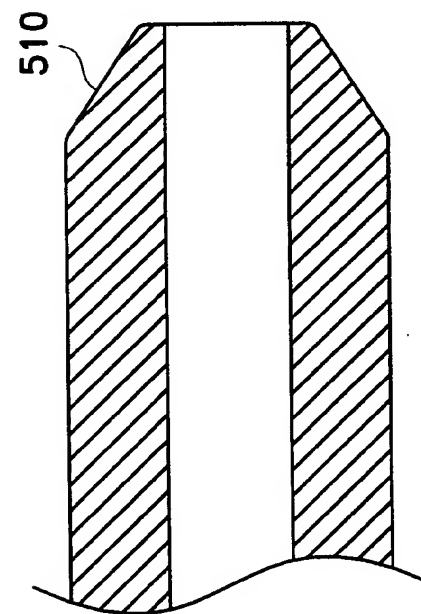


FIG. 5B

# INTERNATIONAL SEARCH REPORT

Int. application No.  
PCT/US95/05438

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61M 5/32  
US CL : 604/265

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/264, 265, 280

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,636,346, (GOLD ET AL.), 13 January 1987. Note the Abstract.	1-29
Y	US, A, 5,045,072, (CASTILLO ET AL.), 03 September 1991. Note Fig. 1.	4-14, 16-25, 27-29
Y, P	US, A, 5,336,205, (ZENZEN ET AL.), 09 August 1994. Note Fig. 1.	4-28
Y	US, A, 5,128,170, (MATSUDA ET AL.), 07 July 1992. Note 1:23-27, 6:61-64, 2:26-35, and 8:58-60.	1-29
A	US, A, 4,537,791, (TARJAN), 27 August 1985. Note Abstract.	30-40
A	US, A, 4,876,126, (TAKEMURA ET AL.), 24 October 1989. Note Abstract.	30-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 JUNE 1995

Date of mailing of the international search report

24 JUL 1995

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